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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,548	02/19/2004	Lee Mizzen	12071-011004	3267

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EXAMINER	
SNYDER, STUART	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 10/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/782,548	MIZZEN ET AL.
	Examiner	Art Unit
	Stuart W. Snyder	1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-89* is/are pending in the application.

4a) Of the above claim(s) *58-89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *53-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/19/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of the Claims

Applicant's election with traverse of Group I in the reply filed on 17 July 2006 is acknowledged. The traversal is on the ground(s) that the Examiner improperly required "further restriction". Applicant argues that the claimed invention is a vaccine with a unique combination of elements rather than a series of unique polynucleotides. This is not found persuasive because neither the concept of combining stress proteins with viral antigens nor the concept of using DNA instead of protein to comprise vaccines is novel (see claims rejection below). The resulting possible combinations, including the 7 influenza proteins specified in claims 53 and 87-89 as well as the 39 generic and specified stress proteins of claims 53 and 55-86, are at least 39^7 that would be an enormous number of sequences to search. The requirement is deemed proper and is therefore made FINAL.

Cancellation of claims 1-52 and submission of new claims 53-89 is acknowledged. Applicant elected Group I, corresponding to claims 53-89, in response to restriction requirements of the Office. Applicant further elected the species consisting of a polynucleotide encoding the fusion protein of hsp 65 and influenza nucleoprotein. No single claim specifies this particular combination so the generic claims 53-57 will be examined; claims 58-89 are withdrawn from consideration. Prior art was not found for this particular combination however it was found for the combination of hsp 70 and influenza nucleoprotein that forms the basis of non-final rejection.

Objection to the Information Disclosure Statements

The PTO Form 1449s filed 19 February 2004 and 2 February 2006 has not been fully considered. This submission cites approximately 183 documents requiring a listing on about 20 pages. In an initial review of 20 U.S. patents and published applications, the Office finds that only 2 of these documents are material to patentability of one or more claims in accordance with 37 CFR 1.56. A review of the first 24 non-patent literature publications revealed none deemed to be material to patentability. In view of the very low percentage of references material to patentability in the sampled documents reviewed, the submission is not in compliance with 37 CFR 1.56 and 1.98. Accordingly, the remaining references will not be considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 53-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for eliciting an immune response in mice against NP using either hsp65 or hsp70, does not reasonably provide enablement for eliciting protective immunity against influenza infection in mammals using influenza protein subunits in combination with other listed stress proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention: The claims are drawn to a vaccine comprising a

polynucleotide that encodes and direct the expression of an antigen of an influenza virus and a stress protein or active portion thereof. Vaccines are defined as:

> Originally, the live v. (vaccinia, cowpox) virus inoculated in the skin as prophylaxis against smallpox and obtained from the skin of calves inoculated with seed virus. Usage has extended the meaning to include essentially **any preparation intended for active immunologic prophylaxis**; e.g., preparations of killed microbes of virulent strains or living microbes of attenuated (variant or mutant) strains; or microbial, fungal, plant, protozoal, or metazoan derivatives or products. (Stedman's Medical Dictionary 27th Edition)

Alternatively:

> 1 : matter or a preparation containing the virus of cowpox or vaccinia in a form used for vaccination
>
> 2 : a preparation of killed microorganisms, living attenuated organisms, or living fully virulent organisms that is administered to **produce or artificially increase immunity to a particular disease** (Webster's Third International Dictionary, Unabridged, Copyright © 1993)

Thus, the normal meaning of the word vaccine, as well as the meaning consistent with the intended use described in the specification (see, for example, page 3, 19-20: "These vaccines are not completely effective in providing protective immunity"). Furthermore, the vaccine is intended for use in mammals. The specification teaches induction of CTL response in mice specific to NP but no other influenza antigens.

State of the prior art: At the time the invention was made, effective anti-influenza vaccines were available using live attenuated or inactivated viruses for approximately 50 years. The vaccines were effective in reducing the morbidity and mortality from 60-90%. Subunit vaccines were being developed but licensed for use in humans (see, for example, Couch RB. Advances in influenza virus vaccine research. Ann N Y Acad Sci. 1993 Jun 23;685:803-12.) Development of alternatives to alum as adjuvant was another

area of active research and included the studies of microbiological stress and toxin proteins (see, for example, Rappuoli R, Pizza M. Novel molecular biology approaches to acellular vaccines. Biotechnol Annu Rev. 1996;2:391-408 and Suzue K, Young RA Heat shock proteins as immunological carriers and vaccines. EXS. 1996;77:451-65.)

Breadth of the claims: The claims are very broad, encompassing a wide range of stress proteins, viral antigens—especially when considering the species variation of influenza virus—and potential vaccine recipients.

Working examples: Three working examples were provided in the specification showing the activity of the compounds of claim 53 in stimulating CTL immune responses to influenza virus NP protein in mice using either hsp 65 or 70. No working examples are disclosed in the specification showing the effectiveness of other influenza viral proteins, other stress-related proteins, or mammalian species.

Guidance in the specification: The specification provides minimal guidance regarding use of the claimed method in construction and use of other putative vaccines instead relying on references to well-known methods in the art; that is an acceptable practice and encouraged by the Office to avoid overly lengthy applications. However, with such a wide variety of viral antigens and stress proteins to combine, guidance for choosing appropriate combinations would be necessary because of the lack of predictability in the art—see below.

Predictability of the art: Vaccinology is well known to be unpredictable. For example, certain subsets of vaccinees do not develop an immune response for which larger segments of the population develop such responses (see, for example, Lambkin R,

Novelli P, Oxford J, Gelder C.Human Genetics And Responses To Influenza Vaccination: Clinical Implications. Am J Pharmacogenomics. 2004;4(5):293-8.). Currently, the reduction in morbidity and mortality in response to influenza vaccination is estimated to be between 60-90%; between 10-40% of the vaccinated population do not mount an effective immune response to an "effective" vaccine.

Amount of experimentation: It is not known whether the claimed compounds have any effect in eliciting protective immunity to the virus in any species other than mice. Although the use of mice is an art-accepted model for vaccine development, other species share more genetic homology with humans and are more predictive of successful vaccination in humans (see, for example, Osterhaus AD, Fouchier RA, Kuiken T. The aetiology of SARS: Koch's postulates fulfilled. Philos Trans R Soc Lond B Biol Sci. 2004 Jul 29;359(1447):1081-2.) Furthermore, given the large number of possible combinations of viral antigens and stress-related proteins, it would be anticipated that a great amount of experimentation would be necessary to determine optimal combinations thereof.

Given the breadth of the claims, the lack of guidance in the specification, and the predictability of the art, it would require undue experimentation for one skilled in the art to use the claimed composition and method. Thus, rejection of claims 53-57 over 35 U.S.C. 112, 1st paragraph because of the overbroad scope of the claims is proper.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 53-57 are rejected under 35 U.S.C. 102(e) as being anticipated by Young (US 6,482,614). The instant application claims a vaccine comprising a polynucleotide that encodes and directs expression of an antigen of influenza virus and a stress protein, and the vaccine induces a cell-mediated cytolytic immune response against the antigen. Further limitations of the claim include the expression of the two proteins (or immunologically active portions thereof) as a fusion protein, that the stress protein is of mycobacterial origin and is hsp65.

Young teaches fusion of a stress protein (either an hsp60 or hsp70 of BCG, see column 17 lines 1-8) and an influenza antigen for use as a vaccine (see especially claims 32 and 33) using a specially designed DNA plasmid. Young further demonstrates that one embodiment of the claimed invention elicits CTL responses in the same strain of mice as Applicants. All of the limitations of the instant Application are found in Young. Therefore, rejection of claims 53-57 under 35 U.S.C. 102(e) as being anticipated by Young is proper.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 53-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roman and Moreno in view of Ulmer, *et al.* Claim 53 is drawn a vaccine comprising a polynucleotide encoding and directing expression of an antigen of influenza virus or antigenic portion thereof and a stress protein; the vaccine inducing a cell-mediated cytolytic immune response against the antigen in a mammal to whom the vaccine is administered.

Roman and Moreno teaches an immunogenic composition comprising a synthetic peptide corresponding to influenza A virus nucleoprotein, residues 106-229 and *M. tuberculosis* hsp70 which elicited peptide-specific proliferative T-cell responses, e.g., a cell-mediated cytolytic immune response. Roman and Moreno does not teach a polynucleotide comprising the composition.

Ulmer, *et al.* teaches the use of polynucleotides as vaccines. Specifically, the teaching is drawn to DNA expression vectors encoding antigenic portions of viral antigen. One example specifically taught the use of a DNA vaccine encoding influenza nucleoprotein that elicited cytotoxic T lymphocytes against the antigen.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of Roman and Moreno by substituting a polynucleotide encoding hsp70 and influenza virus nucleoprotein for the protein components for use as a DNA vaccine as taught by Ulmer, *et al.* The skilled artisan would have been motivated to do so to avoid the difficulty in purifying the proteins from cell culture, to induce a cytotoxic T lymphocyte response, and simplicity of construction

of the vaccine. There would have been a reasonable expectation of success, given the success of other DNA vaccines especially one encoding the influenza nucleoprotein, as taught by Ulmer, *et al.* Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

No claim is allowed. This action is **non-final**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart W. Snyder whose telephone number is (571) 272-9945. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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